

REMARKS

These remarks are in response to the Office Action mailed March 5, 2007. Claims 1 and 4 - 6 have been amended. Claims 3 and 8 - 67 have been canceled without prejudice to Applicant's right to prosecute the canceled subject matter in any divisional, continuation, continuation-in-part or other application. No new matter is believed to have been introduced.

INFORMAL MATTERS

Applicants wish to thank Examiner Ford and her Supervisor for the helpful discussions with Applicants representative on May 14, 2007.

I. OBJECTIONS TO THE CLAIM

Claim 1 is objected to due to the incorrect spelling of "utereric". Applicants note that the amended claim no longer includes the spelling error. Accordingly, the objection may be properly withdrawn.

II. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH***Written Description***

Claims 1 and 3 - 7 stand rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement. This rejection is moot with respect to canceled claim 3. In addition, claims 4 - 7 have been amended to depend from amended claim 1. Applicants respectfully traverse this rejection as it may apply to amended claim 1.

A "clean" copy of amended claim 1 is reproduced below for the convenience of the Examiner:

1. A method of propagating ureteric bud cells in culture, the method comprising:
 - (a) providing a medium not elaborated with cells derived from metanephric mesenchyme (MM) and not containing detectable levels of pleiotrophin, wherein the medium optionally comprises:
 - (i) fibroblast growth factor-1 (FGF1), or a functional equivalent thereof; and
 - (ii) glial derived neutrophic factor (GDNF) , or a functional equivalent thereof;
 - (b) contacting the medium of (a) with exogenous pleiotrophin;

- (c) culturing ureteric bud cells in vitro with the medium of (b) and in the presence of a biocompatible matrix, wherein the cells undergo branching morphogenesis to generate a population of cells comprising tubular branches;
- (d) isolating cells comprising tubular branches; and
- (e) culturing the isolated cells in a biocompatible matrix with the medium of (b).

Applicants note that the recitation of "providing a medium not elaborated with cells derived from metanephric mesenchyme (MM) and not containing detectable levels of pleiotrophin," as set forth in amended claim 1, is inherently supported by the information provided in paragraphs [0047] and [0048] of the application as published (US Patent Application Pub. No. 2005/0074875). The claimed methods are based, in part, on the discovery that morphogenic factors are secreted by metanephric mesenchyme (MM) cells. These cells were generally used to secrete factors in to a medium in order to promote and sustain branching morphogenesis in other cell types, such as ureteric bud cells. The Applicants have fractionated media conditioned by metanephric mesenchyme (MM) cells and have identified factors that promote branching morphogenesis of ureteric bud cells. Paragraph [0047], reproduced below for the convenience of the Examiner, describes the initial phase of identifying such factors.

[0047] The invention demonstrates that UBs undergo branching tubulogenesis in the presence of a **conditioned medium elaborated by a cell line derived from the MM** also isolated from an E11.5 mouse (BSN cells). This suggests that other soluble factors present in BSN-CM are important for UB morphogenesis. These novel factors that are secreted by the MM are important for the development of the collecting system in artificial systems as well as in vivo. (emphasis added)

The information contained in paragraph [0047] demonstrates that medium conditioned by metanephric mesenchyme (MM) cells supports branching morphogenesis. Through chromatographic fractionation of the conditioned medium the Applicants were able to identify at least one of the factors required for branching morphogenesis of ureteric bud cells. This information is provided in paragraphs [0049] and [0050] which are reproduced below for the convenience of the Examiner.

[0049] The invention demonstrates that serial liquid column chromatographic fractionation of BSN-CM contain an active

morphogenetic fraction comprising a single polypeptide (capable of inducing branching morphogenesis comparable to whole BSN-CM).

This polypeptide was identified as pleiotrophin (FIG. 2).

Immunoblot analysis of BSN-CM (FIG. 7A) as well as in situ hybridization data of developing kidney (Vanderwinden et al., 1992), demonstrate that the embryonic MM is a source of pleiotrophin. In addition to its ability to induce branching morphogenesis in the isolated UB, pleiotrophin also induced a UB cell line to form branching tubular structures with lumens, and is thus the only soluble factor so far identified with this capability (FIG. 6). Based on this in vitro data with the isolated UB as well as the UB cell line, the invention provides methods and compositions for use in vitro and in vivo to induce morphogenesis and tubular formation of tissues (e.g., kidney tissue). (emphasis added)

[0050] The invention provides a novel factor, and combination of factors capable of inducing UB branching morphogenetic activity. In one aspect, the invention provides an **18 kDa heparin binding protein**, pleiotrophin, obtained from the BSN-CM. **This factor has not previously been shown to play a role in kidney morphogenesis.** (emphasis added)

Prior to the Applicants discovery that pleiotrophin was secreted by MM cells and required for generating a population of cells that include tubular branches, it was not known which factors were required for branching morphogenesis of ureteric bud cells. Accordingly, the skilled artisan will recognize that a medium which does not initially contain pleiotrophin can be "conditioned" by the addition of exogenous pleiotrophin. In view of the Applicants discovery, the manufacture of a medium that supports ureteric bud cell branching morphogenesis no longer requires exposing the media to MM cells. The language used in amended claim 1 to illustrate this concept is not found *ipsis verbis* in the specification. Nevertheless, in view of the information provided in the specification, the skilled artisan will clearly understand that a medium "not" elaborated with MM cells and "not" containing pleiotrophin can be made suitable for supporting ureteric bud cell branching morphogenesis through the addition of "exogenous" pleiotrophin.

In view of the amendments to the claims and in light of the above discussion, Applicants respectfully request withdrawal of this rejection.

III. REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1 and 3 - 7 stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is moot with respect to canceled claim 3. In addition, claims 4 - 7 have been amended to depend from amended claim 1. Applicants respectfully traverse this rejection as it may apply to amended claim 1.

Applicants have amended claim 1 to clarify the media conditions needed to induce ureteric bud cell branching morphogenesis. The discussion set forth in section II above describes the manner in which the Applicants have identified factors necessary for supporting ureteric bud cell branching morphogenesis. Claim 1 has been amended to clearly identify this subject matter. Accordingly, withdrawal of this rejection is proper and respectfully requested.

IV. REJECTION UNDER 35 U.S.C. §103

Claims 3, 4, 6 and 7 stand rejected under 35 U.S.C. §103, as allegedly unpatentable over Sakurai et al. (PNAS, 1997), in view of "Basic Techniques for Mammalian Cell Tissue Culture" (Current Protocols in Cell Biology, 1998), Naughton et al. (US 2003/0007954), and "Overview of Extracellular Matrix" (Current Protocols in Cell Biology, 1998). This rejection is moot with respect to canceled claim 3. In addition, claims 4 - 7 have been amended to depend from amended claim 1. Accordingly, Applicants submit that this rejection is moot and respectfully request that it be withdrawn.

In summary, for the reasons set forth herein, Applicants maintain that claims 1 and 4 - 7 clearly and patentably define the invention. Applicants request that the Examiner reconsider and withdraw the various grounds for rejection set forth in the Office Action.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' representative can be reached at (858) 509-7318. No fees are believed due. However, should any fees be required, the Commissioner is authorized to charge deficiencies or credit any overpayment to Deposit Account No. 02-4800.

Respectfully submitted,

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Date: May 24, 2007

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